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Hyperuricemia and Incident Hypertension: A Systematic Review and Meta-Analysis

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Abstract

Objective—A novel rodent model and a recent randomized trial of hyperuricemic adolescents with hypertension suggest a pathogenetic role of uric acid in hypertension, but it remains unknown whether these findings would be applicable to adult populations where the larger disease burden exists. We conducted a systematic review and meta-analysis to determine if hyperuricemia was associated with incident hypertension, particularly in various demographic subgroups.

Methods—We searched major electronic databases using Medical Subject Headings and keywords without language restrictions (through April 2010). We included prospective cohort studies with data on incident hypertension related to serum uric acid levels. Data abstraction was conducted in duplicate. We analyzed age, gender, and race subgroups.

Results—A total of 18 prospective cohort studies representing data from 55,607 participants were included. Hyperuricemia was associated with an increased risk for incident hypertension (adjusted risk ratio [RR], 1.41; 95% CI, 1.23–1.58). For 1 mg/dl increase in uric acid level, the pooled RR for incident hypertension after adjusting for potential confounding was 1.13 (95% CI, 1.06–1.20). These effects were significantly larger in younger study populations (p=0.02) and tended to be larger in women (p=0.059). Two studies suggested that the effect may also be larger among black individuals. Furthermore, later publication year and US-based studies were significantly associated with a lower effect estimate (p-values <0.02).

Conclusion—Hyperuricemia is associated with an increased risk for incident hypertension, independent of traditional hypertension risk factors. This risk appears more pronounced in younger individuals and women.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Peter C. Grayson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Keywords

hyperuricemia; hypertension; meta-analysis

INTRODUCTION

Hypertension affects approximately one-third of Americans(1) and is a leading cause of morbidity and mortality.(2) While the etiology of hypertension is unclear in many patients,(3) uric acid has been hypothesized to activate the renin-angiotensin system,(4) which can lead to injury to pre-renal blood vessels.(5) Recently, a novel rodent model of arteriolopathy and hypertension induced by mild hyperuricemia has brought renewed interest into this hypothesis.(5–8) Furthermore, a cross-over randomized trial of 30 hyperuricemic adolescents with hypertension demonstrated that lowering uric acid levels with allopurinol led to lowering blood pressure over a 4-week period.(9) These data support the pathogenetic role of uric acid in the development of hypertension in this specific demographic context, but it remains unknown whether these findings would be applicable to adult populations where the much larger share of hypertension disease burden exists.

To objectively summarize the published data about the relation between hyperuricemia and the risk for incident hypertension, particularly in various demographic subgroups, we performed a meta-analysis of prospective studies on the topic. We hypothesized that in addition to serving as an independent risk factor for incident hypertension in the general population, hyperuricemia may have important differential effects in age, gender, and racial subgroups.

MATERIALS AND METHODS

Literature Search

We searched three major electronic databases — MEDLINE (through April 2010), EMBASE (1980- April 2010), and the Cochrane Library (through April 2010) — using the following heading MeSH terms and keywords: [*uric acid OR hyperuricemia OR urate OR hyperuric$] AND [hypertension OR hypertension, renal OR hypertension, renovascular OR hypertension, malignant OR blood pressure*]. The wildcard character "$" insures that any word that has "hyperuric" at its beginning is included in the search results. We also hand searched bibliographies of identified reports and review articles for additional references.

Study Eligibility and Selection

To be eligible for inclusion, we only considered 1) prospective cohort studies without age restrictions, 2) with longer than one year of follow-up, 3) with a sample size of at least 100 subjects, and 4) an inception cohort free of hypertension. No geographic or language restrictions were applied.

Two authors (PCG and SYK) independently reviewed the studies for final determination of inclusion or exclusion. When multiple articles were published from the same cohort, we selected the reports that contained the most complete and relevant data on the association between hyperuricemia and hypertension.

Data Abstraction and Quality Assessment

All data were independently abstracted in duplicate by two authors (PCG and SYK) using a data abstraction form to retrieve information on study characteristics, participant information, definition of hyperuricemia and hypertension, outcome results, analyses, and

adjustment. Two authors (PCG and SYK) assessed the quality of studies using the Newcastle–Ottawa Scale.(10) This quality score was calculated on the basis of three major components of cohort studies: selection of study groups (0–4 points), comparability of study groups (0–2 points), and ascertainment of the outcome of interest (0–3 points).(10) A higher score represented better methodological quality (Table 1). Areas of disagreement or uncertainty were resolved by discussion.

Statistical Analysis

We converted serum uric acid levels in the studies that used the International system (SI) of units (μmol per liter) into the conventional units (milligram per deciliter), using a conversion rate of 16.81 (1 mg/dL = 59.48 μmol/L).(11)

Pooled estimates of both unadjusted and adjusted risk ratios (RRs) for incident hypertension were calculated using the DerSimonian and Laird random-effects model.(12) This statistical technique weights individual studies by sample size and variance (both within- and between-study variance) and yields a pooled point estimate and a 95% confidence interval (CI). The DerSimonian and Laird technique was considered appropriate because of the relative heterogeneity of the source population in each study. We analyzed hyperuricemia as both a categorical and continuous variable. For studies reporting hyperuricemia as categorical variable, we chose the category nearest to 6.8 mg/dL to define the hyperuricemic group.(13) We preferentially analyzed reported RRs but used raw data to create contingency tables and calculate RRs when not directly reported or when derived from linear trend across category rather than category of interest versus referent category. We added a value of 1 to all counts for those studies that contained a zero count.

We assessed for potential publication bias using the Begg's and Egger's tests and constructed funnel plots to visualize possible asymmetry.(14) To assess for heterogeneity, we calculated the I^2-value, which quantifies the percentage of variability attributable to between-study difference.(15) We performed meta-regression analysis on pooled adjusted and unadjusted RRs to see if any detected heterogeneity could be due to differences in study characteristics using the maximum likelihood method of estimating the additive between-study variance. We evaluated the following study-level characteristics: gender, mean age of study population, length of follow up, publication year, study country, definition of hypertension, and number of adjusted variables (categorized as 0–5; 6–10; >10).

All statistical analyses were done using STATA 11 (Stata Corp, College Station, TX) or SAS 9.1 (SAS Institute, Cary, NC). We followed the Meta-analyses of Observational Studies in Epidemiology guidelines(16) in the report of this meta-analysis.

RESULTS

Study Characteristics

The electronic database search identified 3,923 references. We excluded 3,891 articles based on title or abstract resulting in 34 references for full text review. Review of references of articles selected for full text review and of relevant review articles yielded 2 additional references. A total of 18 prospective cohort studies representing data from 55,607 participants were included in our final review. There were no disagreements between the two reviewers regarding study inclusion (Figure 1).

Table 1 provides characteristics for the 18 included studies. All studies were written in English. Eleven studies were conducted in North America,(2,17–26) four in Asia,(27–30) two in Europe,(31–32) and one in both North America and Asia.(33) Publication dates ranged from 1972 to 2009, whereas lengths of follow-up ranged from 3 to 21 years (average,

8 years). Hyperuricemia was defined on average at a level of 6.2 mg/dL (range, 4.6 – 7.0 mg/dL). Hypertension was typically defined as blood pressure ≥ 140/90 or ≥ 160/95, by self-report, or by use of anti-hypertensive medications.

Hyperuricemia and Incident Hypertension

Twelve studies reported unadjusted RRs of hyperuricemia and incident hypertension.(2,17–18,21,23–29,31,34) The pooled unadjusted RR was 1.81 (95% CI, 1.55–2.07) using the random effects model. There was significant heterogeneity between the studies reporting unadjusted RRs (I^2 = 73.4%, p<0.0001). Eleven studies reported adjusted RRs of hyperuricemia and incident hypertension.(2,18,21–28,33) The pooled adjusted RR was 1.41 (95% CI, 1.23–1.58). There was significant heterogeneity between the studies reporting adjusted RRs (I^2 = 74.5%, p<0.0001) (Figure 2). In all studies that defined urate levels as a categorical variable, the adjusted RR for incident hypertension increased with each successive category of increasing baseline serum uric acid level.

Eleven studies defined urate levels as a continuous variable.(2,19,21–22,24–28,30,32) Six studies defined hyperuricemia per 1mg/dl incremental increase,(2,22,24,26–27,32) and pooled adjusted RR per 1mg/dl increase was 1.13 (95% CI, 1.06–1.20). Eight studies defined hyperuricemia per 1 standard deviation (SD) incremental increase,(19,21–22,24–26,28,30) which ranged from 1.0–1.3 mg/dL. Pooled adjusted RR per 1 SD increase in uric acid level was 1.16 (95% CI, 1.07–1.26).

Analyses for Age, Gender, and Race

We found an inverse relationship between increasing mean study age and log-transformed unadjusted RRs among the eleven studies where this data was available (Figure 3).(2,17–18,21,23–29) Similarly, meta-regression analysis showed that higher mean study age (coefficient −0.03, p=0.02) was significantly associated with a lower effect estimate for the risk of incident hypertension.

Gender-specific RRs were reported for men in nine studies(23–31) including seven limited to men(23–28,31) and for women in four studies(2,24,29–30) including one limited to women.(2) The mean definition of hyperuricemia was 6.44 mg/dL for men and 5.63 mg/dL for women. The summary adjusted RRs of incident hypertension were 1.38 (95% CI, 1.20–1.57) in men and 1.76 (95% CI, 1.46–2.05) in women (Figure 4). Our meta-regression analysis suggested that female gender is associated with a stronger effect on incident hypertension (coefficient 0.25, p=0.059).

Only two studies provided data regarding race as a potential effect modifier of the association between hyperuricemia and incident hypertension which precluded further analysis. Both studies reported the highest adjusted RR in black individuals. One study defined hyperuricemia as a continuous variable (per 1 SD increments),(20) and the other study defined hyperuricemia as a categorical variable.(22)

Other Potential Predictors of Effect Estimates

We performed meta-regression analysis on log-transformed adjusted RRs to investigate heterogeneity of effects across studies. Later publication year (coefficient −0.04, p=0.02) was associated with a significantly lower effect estimate for incident hypertension, while studies conducted outside the United States (coefficient: 0.32, p=0.02) were associated with a significantly higher effect estimate for incident hypertension. Unlike in studies reporting unadjusted RRs, mean study age and gender showed no significant effect on outcome in studies reporting adjusted RRs. Notably, all of these studies adjusted for age and gender within the respective analysis. Length of follow up, definition of hypertension, and number

of adjusted variables were not statistically significant predictors of effect estimates in our analyses.

Publication Bias Assessment

Evidence of publication bias for studies reporting adjusted RRs was noted in the funnel plot (Figure 5) and Egger's test (p=0.03), but not in the Begg's test (p=0.94).

DISCUSSION

In this systematic review and meta-analysis of published prospective studies, we found a modest but significantly increased RR for incident hypertension in subjects with hyperuricemia, independent of traditional risk factors for hypertension. The overall risk for incident hypertension increased by 13% per 1mg/dL increase in serum uric acid level and the risk was more pronounced in younger individuals and in women. Although serum uric acid level of 6.8 mg/dL was used to define hyperuricemia in this analysis, all original studies that employed categorical serum urate levels have reported that the risk of incident hypertension increases with increasing levels of serum uric acid. These data suggest that the relation between serum uric acid levels and hypertension is likely to be linear, rather than being dependent on a specific cut-point or threshold. Overall, these findings provide prospective evidence that individuals with higher serum uric acid, particularly younger adults and women, are at an increased risk for incident hypertension independent of other known risk factors.

Potential mechanisms behind the link between hyperuricemia and development of hypertension have included nitric oxide and renin-angiotensin pathways.(5,35) Uric acid could lead to endothelial cell dysfunction via nitric oxide synthetase(36–38) and stimulate vascular smooth muscle cell proliferation.(7,39) Furthermore, uric acid may also directly stimulate the renin-angiotensin system.(4,40) A recent rodent model of induced hyperuricemia showed that uric acid could cause renal afferent arteriolopathy and tubulointerstitial disease, leading to hypertension.(6) The renal lesions and hypertension were prevented by lowering uric acid levels with allopurinol or benziodarone (a uricosuric agent) and reversed by angiotensin-converting enzyme inhibition.(6)

The stronger association observed among younger individuals is consistent with previous cross-sectional epidemiologic studies that showed a continuous relation of serum uric acid with blood pressure that was stronger in younger individuals and diminished over time.(41–42) Low prevalence of cardiovascular co-morbidities including renal disease in younger subjects may also explain the higher relative risk of hyperuricemia for incident hypertension in this group compared to older subjects. Additionally, children with primary hypertension often have elevated uric acid levels(43) and a recent randomized trial has demonstrated significant reduction of blood pressure and plasma renin activity with urate-lowering therapy in obese adolescents.(9) Experimental animal studies have demonstrated that once significant renal damage occurs, rats develop salt-sensitive hypertension regardless of the uric acid levels.(5) Thus, it is conceivable that hyperuricemia-related pathogenetic mechanisms may be more dominant in earlier stages of hypertension than later stages when salt-sensitivity becomes apparent. At this point, correction of the elevated uric acid level is no longer protective in the aforementioned rodent model of induced hyperuricemia.(44)

Hyperuricemia appears to have a stronger impact among women than among men. This trend would be consistent with gender-specific data from other cardiovascular outcomes. For example, a recent meta-analysis of prospective studies using the outcome of coronary artery disease has found that hyperuricemia is more strongly associated with the risk of coronary heart disease outcome in women.(45) Furthermore, a population based study reported that

the association between gout and acute myocardial infarction was stronger in women than in men.(46) Serum urate levels in men are about 1 mg/dl higher than in women during adulthood, although levels in women increase around natural menopause. Thus, the relative physiologic impact of having gout or a certain level of hyperuricemia may be stronger among women than men.

Similarly, race may be an important effect modifier for the link between hyperuricemia and incident hypertension. Although there were few studies addressing the issue of the race, hyperuricemic black individuals have been suspected of having the highest relative risk for incident hypertension.(20,22) It would be valuable to investigate the impact of race in future studies.

Although we have found an association between hyperuricemia and incident hypertension, this association weakens in recently conducted studies. The forest plot of adjusted RRs (Figure 3) demonstrates that effect estimates approach the null in more recent studies. Additionally, meta-regression shows that later publication year predicts lower risk for incident hypertension. While one could suggest that later studies may have been of better quality, our quality scores of both earlier and later studies were consistently high. It is also conceivable that later studies tended to adjust for more covariates, and some of these covariates might have been at the causal pathway of interest (e.g. biomarker correlates). Thus, some of these adjustments might have led the effect estimates towards the null.

Interestingly, studies conducted outside of the US were associated with a higher effect estimate for incident hypertension than those done in the US. Although we attempted to minimize bias by imposing no geographic or language restrictions to our search strategy, all articles identified for inclusion were written in English. While the difference may represent a type of publication bias based on country-of-origin,(47) the difference may also reflect a biological divergence from different populations.

It remains unclear whether uric acid has a causal role in correlated metabolic conditions, such as insulin resistance and obesity(48). Nevertheless, all studies included in our meta-analysis that reported adjusted RRs controlled for adiposity (i.e. BMI or abdominal circumference) and most of the included studies adjusted for some measure of insulin resistance. If obesity or insulin resistance lies on a causal pathway between hyperuricemia and hypertension, then adjusting for these variables could bias the effect estimates towards the null. Given the increasing worldwide prevalence of obesity and metabolic syndrome in recent decades(49) and the high burden of these conditions in the US(50), adjusting for adiposity and insulin resistance might explain why there were lower effects estimates in studies conducted more recently and based on US populations. Interestingly, among studies reporting unadjusted RRs, publication year and study country showed no significant effect.

Several potential limitations inherent to meta-analysis of observational studies should be noted. First, even with our comprehensive search strategy, Egger's test and the funnel plot suggested potential publication bias. While the rank-based Begg test did not find evidence of publication bias, this test tends to have lower power to detect publication bias. These test results do not allow us to gauge the degree of exaggeration in the pooled value. However, given that the largest studies(22,26) indicate statistically significant increases in risk due to hyperuricemia, the increase in risk is likely real, although its magnitude may be overestimated. Second, statistical methods and degree of adjustment differed slightly in each study. Consequently, we performed separate analyses for hyperuricemia as both a continuous and categorical variable, we evaluated both unadjusted and adjusted RRs, and we selected the best adjusted RR per individual study. Third, in observational studies there is potential for bias from unmeasured confounding. Finally, although we focused on

prospective studies, we cannot eliminate the potential for reverse causation (i.e. changes from pre-clinical hypertension leading to hyperuricemia).

Our study has several important strengths. We selected large-scale, prospective studies with inception cohorts free of disease, which helped precision of our estimates while minimizing heterogeneity. Furthermore, we evaluated the quality of observational studies with the Newcastle-Ottawa scale,(16) which scores the three most important domains of prospective cohort studies: selection of study participants, measurement of exposures and outcomes, and control of confounding. We also sought gender-specific analyses of the studies while adjusting for traditional hypertension risk factors. Finally, we performed meta-regression analysis to evaluate several potential sources of heterogeneity between studies.

In conclusion, our meta-analysis of published prospective studies indicates that hyperuricemia is associated with an increased future risk of incident hypertension, independent of other risk factors. This risk appears more pronounced in younger individuals and women. These data expand on well-established, cross-sectional associations between hyperuricemia and hypertension, and extend the link to the future risk of hypertension. Whether this link is causal remains to be clarified further by future studies. In particular, randomized trial data on the effect of urate-lowering medications on the prevention or treatment of hypertension, with particular attention paid to gender, age, and racial subgroups, would be valuable to clarify this question.

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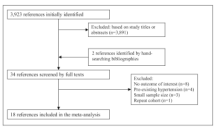

Figure 1.
Study selection flow diagram.

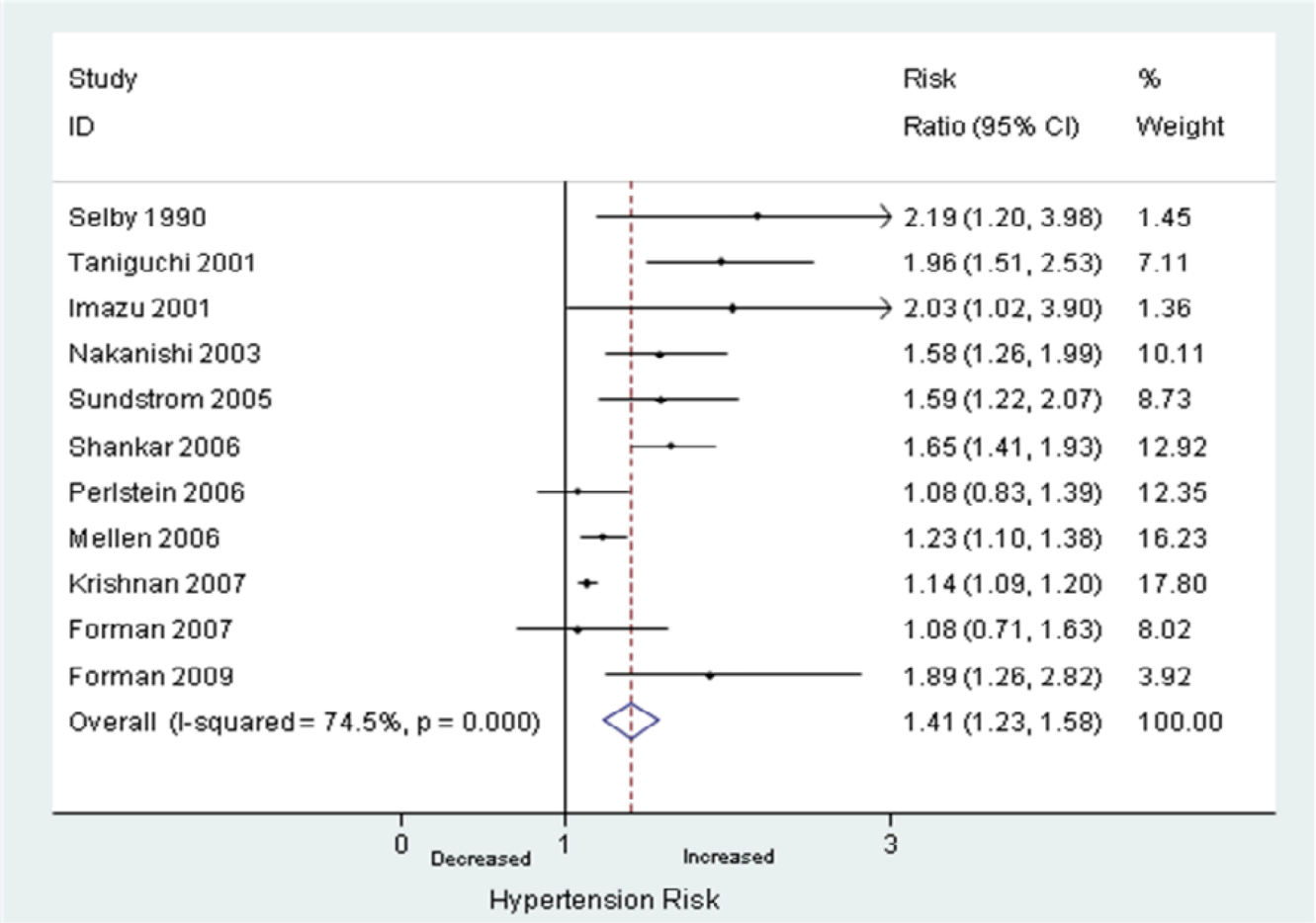

Figure 2.
Random-effects analysis of adjusted risk ratios of hyperuricemia associated with incident hypertension.

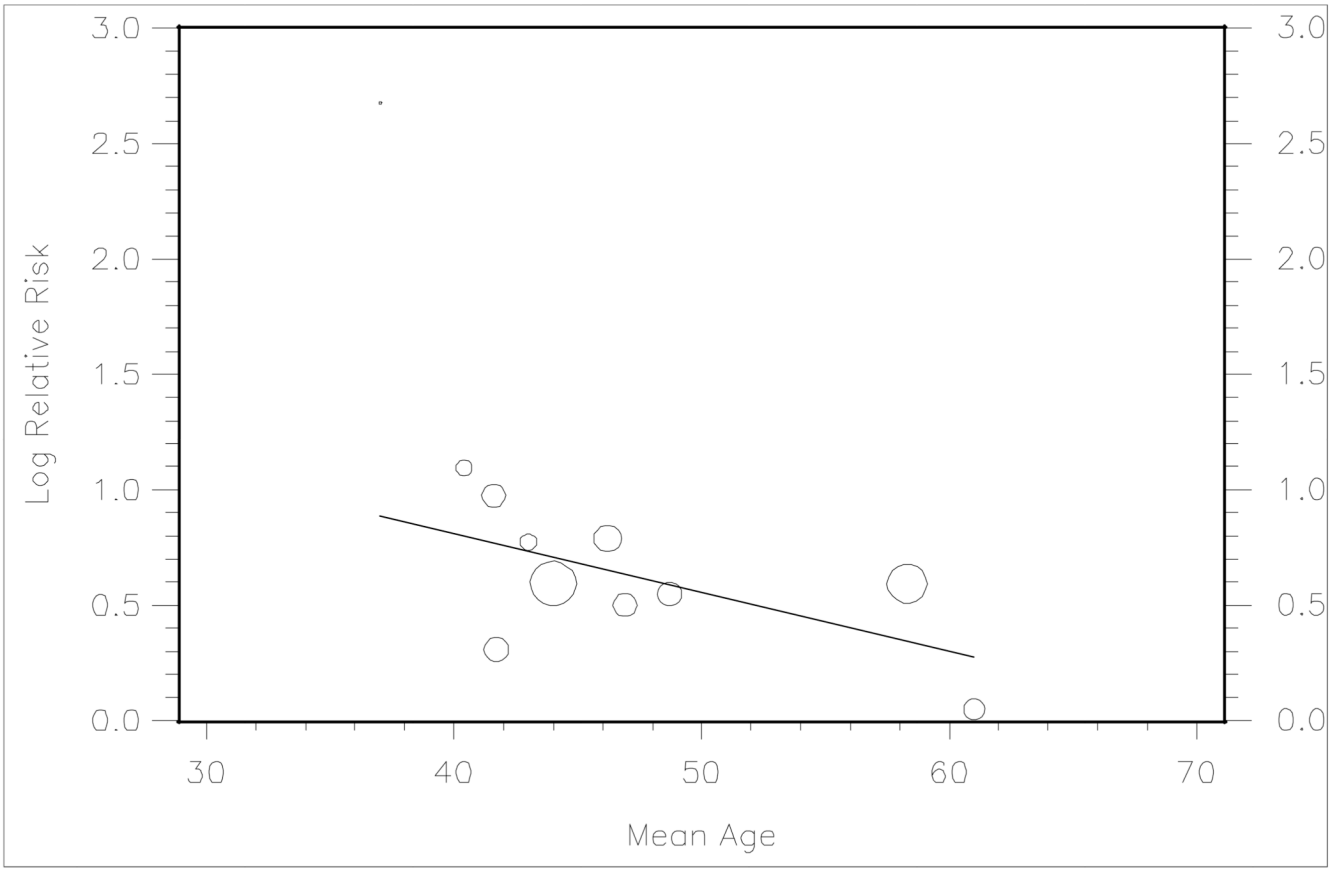

Figure 3.
Random effects determined meta-regression line (β1= −0.026, p=0.02) of reported unadjusted risk ratios versus mean study age in 11 studies. Bubble size represents sample size.

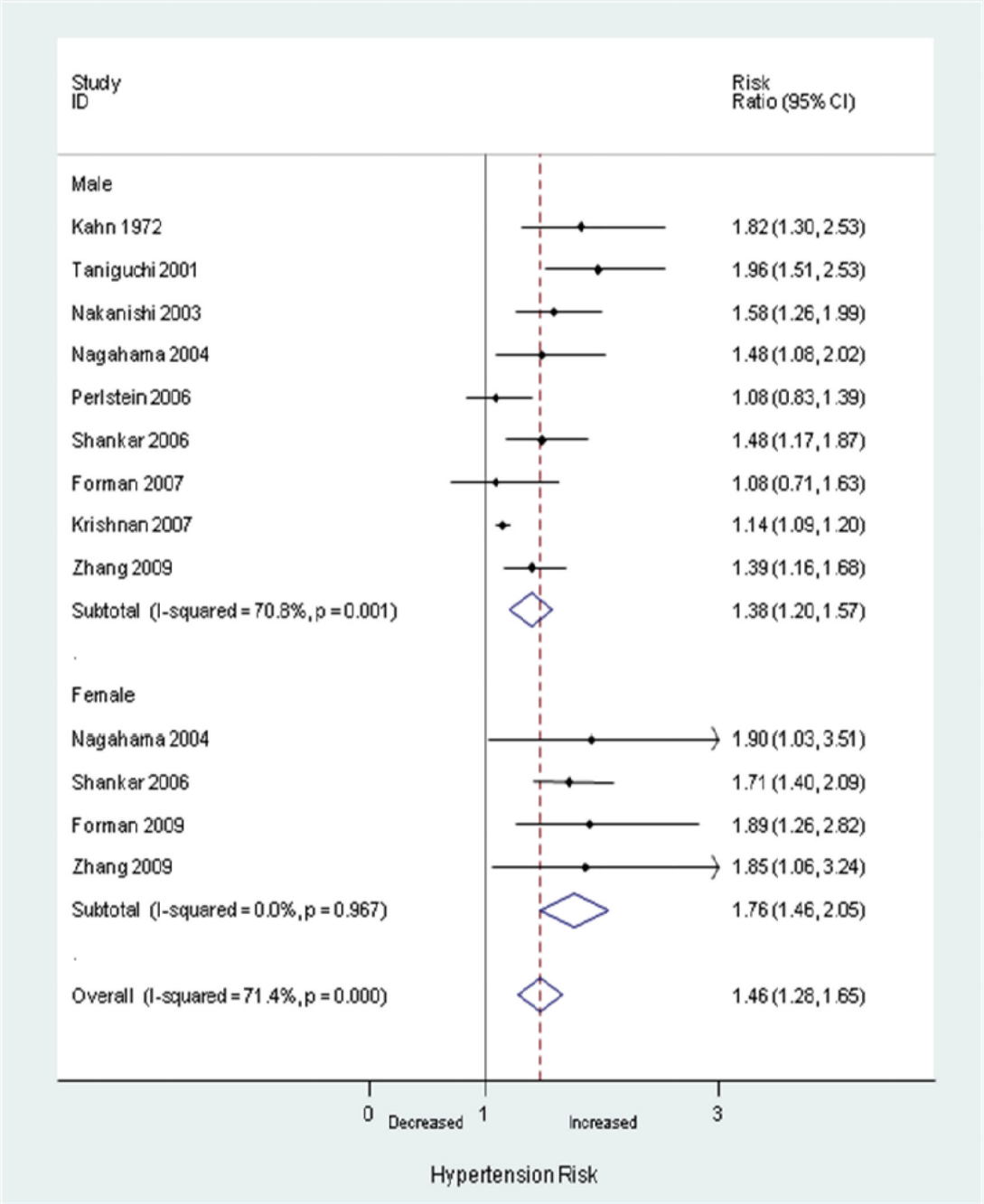

Figure 4.
Random-effects analysis of gender-specific adjusted risk ratios of hyperuricemia associated with incident hypertension.

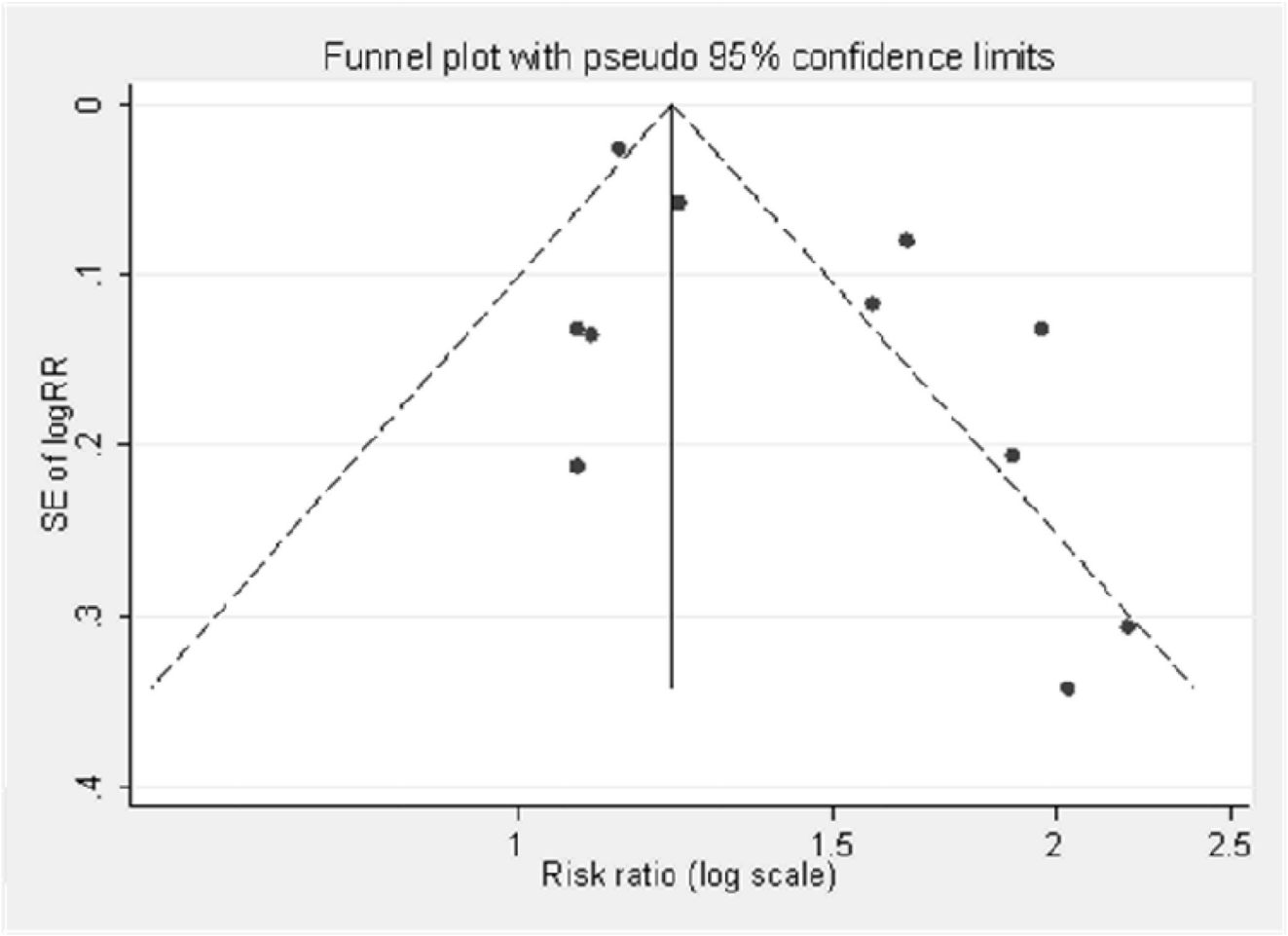

Figure 5.
Funnel plot for publication bias in 11 studies reporting adjusted risk ratios of hyperuricemia associated with incident hypertension. Dashed lines indicate 95% confidence intervals. SE: standard error, RR: risk ratio.

Table 1

Study Characteristics

Study name, Publication year	Country, Cohort	Study population (% men)	Age (mean)	Follow-up (yr)	Hyperuricemia definition (mg/dl)	Hypertension definition	Variables controlled (No.)	Quality assessment score[§]
Forman 2009(2)	USA, NHS	1496 (0)	43	8	4.6	Self report	activity, age, BMI, chol, etoh, FH, GFR, homocysteine, insulin, sICAM,smoke, TG (12)	4/2/2
Zhang 2009(30)	China, Quinadao Port Health Study	7220 (73.8)	37	4	5.7 (M) 4.8 (F)	>/= 140/90, meds	activity, age, BMI, chol, circumference, DBP, etoh, FH, glc, HDL, salt, SBP, smoke, TG (14)	4/2/3
Forman 2007(25)	USA, HPFS	1454 (100)	61	8	6.8	Self report	activity, age, BMI, DBP, etoh, FH, GFR, race, SBP, smoke, weight change (11)	4/2/2
Krishnan 2007(26)	USA, MRFIT	3073 (100)	44	6	7.0	>/= 140/90, meds	age, BMI, creatinine, chol, DBP, etoh, proteinuria, SBP, smoke (9)	3/2/3
Mellen 2006(22)	USA, ARIC	9104 (45.5)	53.3	9	7.0	>/= 140/90, meds	age, BMI, DBP, DM, GFR, location, SBP, smoke (8)	4/2/2
Perlstein 2006(23)	USA, NAS	2062 (100)	41.7	21.5	7.0	>/= 160/95, meds	age, chol, circumference, DBP, etoh, glc, SBP, smoke, TG (9)	4/2/3
Shankar 2006(24)	USA, Beaver Dam Eye Study	2520 (43.7)	58.3	10	6.6	>/= 140/90, meds	A1C, activity, age, BMI, chol, DBP, DM, education, etoh, GFR pulse, SBP, sex, smoke (14)	4/2/3
Sundstrom 2005(21)	USA, Framingham	3329 (44.4)	48.7	4	6.4	>/= 140/90, meds	age, BMI, cardiac meds, creatinine, DBP, DM, etoh, GFR, proteinuria, SBP, sex, smoke, weight change (13)	4/2/3
Nagahama 2004(29)	Japan, OGHMA	4489 (65.2)	46.9	3	7.0 (M) 6.5 (F)	>/= 140/90	age, chol, DM, etoh, FH, HDL, obesity, smoke, TG (9)	4/2/3
Nakanishi 2003(28)	Japan, Japanese Office Workers	2310 (100)	46.2	6	6.7	>/= 140/90, meds	activity, age, BMI, chol, etoh, fasting glc, FH, HDL, MBP, smoke, TG (11)	4/2/3
Imazu 2001(33)	USA/Japan, Hawaii – LA – Hiroshima Study	159 (35.7)	54.8	15	6.0	>/= 160/95, meds	age, BMI, change BMI, chol, fasting glc, insulin, SBP, sex, TG (9)	3/2/2
Taniguchi 2001(27)	Japan, Osaka Work Site	6356 (100)	41.6	9.7	6.2	>/= 160/95	activity, age, BMI, etoh, duration of walk to work, fasting glc, smoke (7)	4/2/3
Dyer 1999(20)	USA, CARDIA	4747 (44.9)	24.7	10	Continuous	>/= 140/90, meds	activity, age, circum-ference, etoh, education, HDL, insulin, pulse, SBP, smoke, TG (11)	4/2/3
Jossa 1994(32)	Italy, Olivetti Heart Study	505 (100)	36.2	12	Continuous	>/= 140/90, meds	age, BMI, chol, TG's (4)	4/2/3
Hunt 1991(19)	USA, Utah Cardiovascular Genetics Clinic	1482 (97.3)	34.4	7	Continuous	Initiation of anti-hypertensive meds in clinic	age, BMI, SBP sex (4)	3/2/2

Study name, Publication year	Country, Cohort	Study population (% men)	Age (mean)	Follow-up (yr)	Hyperuricemia definition (mg/dl)	Hypertension definition	Variables controlled (No.)	Quality assessment score[§]
Selby 1990(18)	USA, Kaiser Permanente	2062 (39.3)	40.4	6	Quintile 5	>/= 160/95, meds	age, BMI, DBP, etoh, FH, salt, SBP (7)	4/2/3
Fessel 1973(17)	USA, Target Population and Screening Program	335 (55)	37	5	2 SD from matched mean	>/= 150/95	Unadjusted (0)	3/0/3
Kahn 1972(31)	Israel, Israeli Heart Study	2904 (100)	40–60+	5	5.0	>/= 160/95	age, area of birth (2)	3/0/3

Abbreviations - NHS: Nurses' Health Study, HPFS: Health Professionals Follow-up Study, MRFIT: Multiple Risk factor Intervention Trial, ARIC: Atherosclerosis Risk in Communities, NAS: Normative Aging Study, OGHMA: Okinawa General Health Maintenance Association, CARDIA: Coronary Artery Risk Development in Young Adults, A1C: hemoglobin A1C, ACTIVITY: physical activity level, BMI: body mass index, CHOL: cholesterol, CIRCUMFERENCE: waist circumference, DBP: diastolic blood pressure, DM: diabetes mellitus,ETOH: alcohol use, FH: family history, GFR: glomerular filtration rate, GLC: glucose, HDL: high-density lipoprotein, INSULIN: fasting insulin, MBP: mean blood pressure, SALT: dietary salt intake, SBP: systolic blood pressure, sICAM: soluble intracellular adhesion molecule, SMOKE: tobacco use,. TG: triglycerides.

[§]Derived from the Newcastle-Ottawa Scale for Cohort Studies(10).